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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,288	11/28/2000	Dale B. Schenk	15270J-004765US	9431

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EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/724,288	SCHENK ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90-94,96-98 and 100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-94,96,97 and 100* is/are rejected.

7)☒ Claim(s) *98* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/28/03; 12/21/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claim 92 has been amended as requested in the response filed December 21, 2006. Claims **90-94**, **96-98**, and **100** are pending and under examination in the current office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

A signed and initialed copy of the IDS paper submitted 21 December 2006 is enclosed in this action.

Withdrawn Objections and Claim Rejections

Specification

The objection to the specification regarding the invention's title is withdrawn in view of Applicant's amendment to the title.

The rejection of claim 92 under 35 U.S.C. 112, second paragraph, as set forth at p. 4 of the previous (06/21/2006) office action is withdrawn in view of applicant's amendment to the claim.

The declaration filed on December 21, 2006 under 37 CFR 1.131 is sufficient to overcome the Brazil et al. reference. Accordingly, the rejection of claims 90-92, 94, 96, and 97 under 35 U.S.C. 102(a) is hereby withdrawn. The rejection of claims 90-94, 96-98 and 100 under 35 U.S.C. 103(a) as being unpatentable over Brazil et al. in view of DeWitt et al. and WO 99/60024, and further in view of Johnson-Wood et al., Friedland et al., and Walker et al. is similarly withdrawn.

Applicant's arguments, see p. 7 in particular, filed December 21, 2006, with respect to the rejection of claims 90-94, 96-98 and 100 under 35 U.S.C. 103(a) have been fully considered and are persuasive. The rejection of claims 90-94, 96-98 and 100 under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,935,927 to Vitek et al. in view of DeWitt et al. and WO 99/60024, and further in view of Johnson-Wood et al., Friedland et al. and Walker et al. has been withdrawn.

New Claim Rejections

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 90-94, 96, 97 and 100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening an anti-Aβ antibody for activity in antibody-mediated clearance of an amyloid deposit of Aβ, does

not reasonably provide enablement for a method of screening any antibody for such activity as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are broadly drawn to a method of screening an antibody for activity in clearing an amyloid deposit of Aβ, comprising combining the amyloid deposit, the antibody, and microglial cells *in vitro*, and monitoring a reduction in the amount of amyloid deposit remaining, wherein a reduction indicates the antibody has clearing activity against the amyloid deposit. The claims are thus drawn to the use of a genus of non-specific antibodies for practicing the screening method.

The nature of the invention is the demonstration that certain anti-Aβ antibodies, in particular those antibodies that bind to an epitope within Aβ1-7, are capable of inducing a phagocytic clearance response to amyloid deposits *in vitro* by microglial cells. Both the instant application and the art recognize that such an *ex vivo* assay may be used as a predictor of the antibody's *in vivo* efficacy in potential therapeutic use, such as in the treatment of Alzheimer's disease. See, for example, Bard et al. (*Nat*

Med. 2000; 6(8): 916-919) and Bard et al. (*Proc Natl Acad Sci USA*, 2003; 100(4): 2023-2028), both listed on Applicant's IDS. However, both the instant specification and the art indicate that only anti-Aβ antibodies, and in particular those anti-Aβ antibodies directed to the N-terminus of Aβ such as residues 1-7 of Aβ, have *ex vivo* efficacy. For example, the instant application discloses that control antibodies were incapable of inducing a clearance response, such that "there were no phagocytic vesicles containing Aβ, and the plaques remained intact within the section" (see p. 98, lines 14-16). Similarly, Bard et al. (2000) note that in the *ex vivo* assay, "there was no degradation of Aβ staining in cultures with control IgG1" (see p. 918, 2nd column). Thus, the instant disclosure is lacking in guidance or evidence that any antibody, such as a non-anti-Aβ antibody, would be capable of performing the required activity. Applicant's disclosure is limited to findings on anti-Aβ antibodies only. The specification fails to provide sufficient guidance as to whether said screening method could be practiced on non-related antibodies, such as an anti-myelin antibody, an anti-tau antibody, or an anti-neuron-specific antibody to name but a few.

The state of the art also indicates that even within anti-Aβ antibodies, there is unpredictability as to which of the antibodies will elicit a phagocytic response. For example, Bard et al. (2000) note that antibodies 16C11 and 21F12, which both recognize C-terminal epitopes of Aβ, are ineffective in mediating an *ex vivo* clearance response (see Table 1, p. 918). Similarly, Ard et al. (*J. Neurosci Res*, 1996; 43:190-202) note that when 10% fetal bovine serum (which comprises various IgG molecules) was added to medium containing cultured microglia and Aβ aggregates, a decrease in

phagocytic activity was observed. While the investigators surmised that the suppression in microglial activity may be due to proteases within the serum, the possibility that interference from non-specific IgG molecules in the serum cannot be ruled out as a potential cause of decreased Aβ accumulation in the microglial. Thus the art reflects unpredictability in performance of clearance activity when the three main components – an antibody, an amyloid deposit, and microglial cells – are simply combined *in vitro* without regard to the specificity of the antibody. As such it would require undue experimentation on the part of the skilled artisan to screen the genus of nonspecific antibodies in the claimed method, not all of which would be at all efficacious.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentech Inc, v. Novo Nordisk*, 42 USPQ 2d 100, (CAFC 1997), the court held that: "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". The instant

specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Due to the breadth of the claims encompassing a genus of non-specific antibodies, the state of the prior art which establishes the unpredictability of eliciting a phagocytic response even when anti-Aβ-specific antibodies are used, and the complex nature of the invention, undue experimentation would be required of the skilled artisan to practice the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, second paragraph

Claim 90 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: comparing the reduction in the amount of the amyloid deposit to a control sample or culture.

Claims 90 and 91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrases "screening an antibody for activity in clearing an amyloid deposit" and "indicating the antibody has clearing activity against the amyloid-deposit" in claim

90 render the claim ambiguous and indefinite because it would appear that the antibody itself is responsible for clearing the amyloid deposits when in fact it is the microglial cells that phagocytose the amyloid deposits. It is presumed, therefore, that the activity of the antibody is to enhance the microglial cells' phagocytic clearing activity toward amyloid deposits of Aβ.

Regarding claim 91, the recitation of "an antigen" renders the claim indefinite because it is unclear which antigen is being monitored in the claimed method. For example, the claim recites "monitoring the amount of an antigen associated with the amyloid deposits". However, the claim 90 recites a method of screening an antibody for "activity in clearing an amyloid deposit of Aβ". It is therefore unclear whether this antigen being monitored is Aβ or it is another undefined antigen. The metes and bounds of the claim therefore cannot be determined.

Conclusion

Claims 90-94, 96, 97 and 100 are rejected. Claim 98 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Kimberly Ballard, Ph.D.
April 14, 2007

ELIZABETH KEMMERER
PRIMARY EXAMINER